Practitioner's Docket No. U013943-5
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Amarjit SINGH, et al.
Application No.: 10/089,020 Group No.: 1616
Filed: March 27, 2003 Examiner: A. N. Pryor
Confirmation Number: 9010

For: CONTROLLED RELEASE COMPOSITIONS COMPRISING NIMESULIDE

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

NOTE: The phrase "the date on which" an "appeal was taken" in 35 U.S. C. 154(b)(1)(A)(ii) (which provides an adjustment of patent term if there is a delay on the part .of the Office to respond within 4 months after an "appeal was taken") means the date on which an appeal brief under § 1.192 (and ,not a notice of-appeal). was filed. Compliance with § 41.37 requires that. 1. the appeal brief fee (§ 41.20(b)(2)) be paid (§ 41.37(x)(2)); and 2. the appeal brief complies with §§ 41.73(c)(i)-(x). See Notice of September 18, 2000, 65 Fed. Reg. 56366, 56385-56387 (Comment 38).

1. Transmitted herewith is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on April 1, 2010

NOTE: Appellant must file a brief under this section within two months from the date of filing the notice of appeal under § 41.31. 37 CFR 41. (a)(1). The brief is no longer required in triplicate. The former alternative time for filing a brief (within the time allowed for reply to the action from which the appeal was taken) has been removed. Appellant must file within two months from the notice of appeal. See Notice of August 12, 2004, 69 FR 49960, 49962.

CERTIFICATE OF MAILING/TRANSMISSION (37 CFR 1.8a)

I hereby certify that this correspondence is, on the date shown below, being:

MAILING

☐ deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450

FACSIMILE

☐ transmitted by facsimile to the Patent and Trademark Office to **(571) 273-8300**

EFS-WEB

■ transmitted electronically

Signature

Date: October 29, 2010

Janet I. Cord
(type or print name of person certifying)

2. STATUS OF APPLICANT

This application is on behalf of

■ other than a small entity

☐ a small entity.

A statement:

☐ is attached.

☐ was already filed.

3. FEE FOR FILING APPEAL BRIEF

Pursuant to 37 C.F R. § 41.20(b)(2), the fee for filing the Appeal Brief is:

☐ small entity $270.00

■ other than a small entity $540.00

Appeal Brief fee due $ 540

4. EXTENSION OF TERM

NOTE: 37 CER. §: 1.704(b) ". .. .an applicant shall be deemed to have failed to engage in reasonable efforts to conclude processing or examination of an application for the cumulative total of any periods of time in excess of three months that are' taken to reply to any notice or action by the Office making any rejection, objection, argument, or other request, measuring such three-month period from the date the notice or action was mailed or given to the applicant, in which case the period of adjustment set forth in § '.1.703 shall be reduced by the number of days, if any, beginning on the day after the date that is.. three months after the date of mailing or .transmission of the Office communication notifying the applicant of the .rejection,,. objection,. argument, or other request and ending on the date the reply was filed. The period, or shortened statutory period, for reply that is set in the, Office action or notice has no effect on the three-month period set forth in this paragraph. "

NOTE: The time periods set forth in 37 C FR. § 1.192(a) are subject to the provision of § 1.136 for patent applications. 37 CFR. § 1.191(d). See also Notice of November 5, 1985 (1060 O. G. 27).

NOTE: As the two-month period set in § 1.192(a) for filing an appeal brief is, not subject to the six-month maximum period specified in 35 U.S. C. § 133, the period for filing an appeal brief may be extended up to seven months. 62 Fed. Reg. 53,131, at 53,156; 1203 O.G. 63, at 84 (Oct. 10, 1997).

■ The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136,apply.

WARNING: The provisions of 37 CFR § 1.136 do not apply in an ex parte reexamination. Any requests for extension must be made pursuant to 37 CFR 1.550(c).

(complete (a) or (b), as applicable)

(a) ■ Applicant petitions for an extension of time under 37 C.F.R. 1.136 (fees: 37 C.F.R. 1.17(a)(1)-(5)) for the total number of months checked below:

	Extension (months)	Fee for other than small entity	Fee for small entity
☐	one month	$ 130.00	$ 65.00
☐	two months	$ 490.00	$ 245.00
☐	three months	$ 1,100.00	$ 555.00
☐	four months	$ 1,730.00	$ 865.00
■	five months	$ 2,350.00	$ 1,175.00

Fee $ 2350

If an additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

☐ An extension for _____ months has already been secured. The fee paid therefor of $ _____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $ _____

OR

(b) ☐ Applicant believes that no extension of term is required. However, this is a conditional petition being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition for extension of time.

5. TOTAL FEE DUE

The total fee due is:

■ Appeal brief fee $ 540

■ Extension fee (if any) $ 2350

TOTAL FEE DUE $ 2890

6. FEE PAYMENT

Attached is a check in the sum of $_____.

■ Charge Account No. 12-0425 the sum of $ 2890_____ .

☐ Charge any additional fees required by this paper or credit any overpayment in the manner authorized above.
A duplicate of this paper is attached.

7. FEE DEFICIENCY

NOTE: If there is a fee deficiency and there is no authorization to charge an account, additional fees are necessary to cover the additional time consumed in making up the original deficiency. If the maximum six-month period has expired before the deficiency is noted and corrected, the application is held abandoned. In those instances where authorization to charge is included, processing delays are encountered in returning the papers to the PTO Finance Branch in order to apply these charges prior to action on the cases. Authorization to change the deposit account for any fee deficiency should be checked. See the Notice of April 7, 1986, 1065 O.G. 31-33.

☒ If any additional extension and/or fee is required, charge Account No. 12-0425.

AND/OR

☒ If any additional fee for claims is required, charge Account No. 12-0425

AND/OR

☒ Refund any overpayment to Account No. 12-0425.

Reg. No.: 33778

Tel. No.: (212) 708-1935

Customer No.:
00140
PATENT TRADEMARK OFFICE

SIGNATURE OF PRACTITIONER

Janet Cord

(type or print name of practitioner)

P.O. Address

c/o Ladas & Parry LLP
26 West 61st Street
New York, N.Y. 10023

Practitioner's Docket No. U 013943-5 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Amarjit **SINGH**, et al.

Serial No.: 10/089,020 Group No.: 1616

Filed: March 27, 2003 Examiner: A.N. Pryor

Confirmation No.: 9010

For: CONTROLLED RELEASE COMPOSITIONS COMPRISING NIMESULIDE

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

ATTENTION: DO/US

Optional Customer No. Bar Code

00140
00140
PATENT TRADEMARK OFFICE

Date of this paper: October 29, 2010

APPLICANTS' BRIEF ON APPEAL

TABLE OF CONTENTS

(i) Real Party of Interest

The real party of interest is Panacea Biotec Limited Assignment Recorded March 27, 2003 at Reel: 014021, Frame: 0663.

(ii) Related Appeals and Interferences

There are no prior or pending appeals, judicial proceedings, or interferences known to Appellant which are related to, directly affect or are directly affected by or have a bearing on the Board's decision in the pending appeal.

(iii) Status of claims

Claims 1, 5, 8-11, 19, and 25 have been rejected multiple times and are the subject of this appeal. Claims 2–4, 6, 7, 12-18, 20-24 and 27-31 are cancelled.

Claim 26 is allowed.

(iv) Status of Amendments

All amendments have been entered.

(v) Summary of Claimed Subject Matter

Unless otherwise specified, all page and line numbers in this section are those of the current application.

The present invention is directed to a once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises 200mg micronized nimesulide having average particle size below 5 microns wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable and a process for making a once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises 200mg micronized nimesulide having average particle size below 5 microns wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable.

The invention defined by independent Claim 1 is a once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises 200mg micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more release controlling materials in an amount from 8% to 20% w/w to control the release of said micronized nimesulide from said composition and pharmaceutical excipients from 30% to 60% w/w of the tablet composition, wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are

biodegradable and are selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.

Claim 5 depends from Claim 1 and defines the composition as claimed in Claim 1, that further comprises release modifiers selected from the group consisting of wetting agents, solubilizers, surfactants, plasticizers, pore formers, pH modifiers and tonicity adjusting agents.

Claim 8 also depends from Claim 1 and defines that the extended release layer further comprises polymers, selected from the group consisting of polycarbophils, carbomers, alginates, cellulose and cellulose derivatives, chitosan gums and lecithins.

Claim 9 depends from Claim 5 and defines that when the release modifier is a pH modifier and is selected from the group consisting of sodium bicarbonate, hydrochloric acid, citric acid, malic acid, and tartaric acid.

Claim 10 also depends from Claim 5 and defines that the tablet composition as claimed in Claim 5, the release modifier is selected from the group consisting of fats, fatty acids and transesterification products of fats and fatty acids with polyols.

The invention of Claim 11 is a process for the manufacture of a once- a-day controlled release tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises mixing together micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more release controlling materials in an amount from 8% to 20% w/w to control the release of said micronized nimesulide from said composition and pharmaceutical

excipients from 30% to 60% w/w of the tablet composition, wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable and are selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.

Claim 19 also depends from Claim 1 and further defines that the single unit fast release layer comprises micronized nimesulide having average particle size below 5 microns and one or more pharmaceutical excipients selected from diluents, binders, wetting agents, disintegrants and lubricants; and the single unit extended release layer comprises micronized nimesulide having average particle size below 5 microns and biodegradable release controlling material selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.

The invention of Claim 25 is a once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a coating, a single unit fast release layer and single unit extended release layer, which comprises 200 mg micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more release controlling materials in an amount from 8% to 20% w/w to control the release of said micronized nimesulide from said composition and pharmaceutical

excipients from 30% to 60% w/w of the tablet composition, wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable and are selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.

(vi) Grounds of Rejection to be Reviewed on Appeal

Whether Claims 1, 5, 8-11, 19 and 25 are unpatentable under 35 U.S.C. 103(a) over Skinhoj et al (US 6599529; 7/29/03), Saslawski et al. (WO 99/33448; 7/8/99) in view of Gibson et al. (US 6426340; 7/30/02) based on US Provisional 60/018202; 5/23/96)?

(vii) Argument

This application was filed with the US Patent and Trademark Office on March 25, 2002. There have been numerous official actions issued. Multiple interviews have been conducted with the Examiner in order to explain to the Examiner that the claims define a patentable invention that is neither anticipated nor obvious over any of the references that were cited by the Examiner during prosecution of this application. Furthermore, applicants have submitted with the responses, declarations and literature references as evidence of patentability of the claimed invention including evidence of commercial success. A description of the extended prosecution of this application is found in Appendix (xi) Prosecution History Appendix.

The rejection under 35 USC 103(a) is to be reversed. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR,* at 1396. In this case, there is no rational basis to support the Examiner's assertion that applicants' invention would be obvious in view of Skinhoj et al (US 6599529; 7/29/03), Saslawski et al. (WO 99/33448; 7/8/99) in view of Gibson et al. (US 6426340; 7/30/02) based on US Provisional 60/018202.

The combination of Saslawski (WO '448) and Skinhoj ('529) do not teach, suggest or provide one of skill in the art with the motivation to prepare a composition as claimed in Claims 1, 5, 8-10, 19, and 25 or to develop the process of Claim 11.

These references do not teach, suggest or provide one of skill in the art with the

motivation to prepare a composition wherein the release controlling materials in the extended release layer are biodegradable.

Further, these references do not teach, suggest or provide one of skill in the art with the motivation to prepare a once-a-day controlled release tablet composition for peroral administration consisting of a single unit fast release layer and a single unit extended release layer wherein micronized nimesulide having average particle size below 5 microns is present in the fast release layer and the extended release layer.

Saslawski et al. teach a multilayer tablet that can be made up of two layers i.e. a first outer layer (immediate or fast release layer) and second layer in contact with the first layer (prolonged release layer containing a **nonbiodegradable, inert porous polymeric matrix** in which the active substance is dispersed). See page 2, lines 19-30. Saslawski et al. teach that the second layer constitutes an inert matrix that does not become eroded and does not swell in an aqueous medium (See page 3, line 33-35) and that the essential constituents of the second prolonged-release layer are polymeric materials which confer on it **its inert and nonbiodegradable character**. The polymers or copolymers are insoluble in water, not forming a gel and are discharged intact by the body (See page 12, lines 10-15).

Saslawski et al. discloses specifically the use of **nonbiodegradable inert material** in the second layer and **not biodegradable material** as included in independent claims 1, 11, and 25. Contrary to what the Examiner states on page 8, lines 4-5 in the Official Action of December 18, 2009 ("The Examiner reiterates that there is no recitation in the instant claims that the release controlling material is biodegradable."), the term "biodegradable" was present in line 9 of Claims 1, 11 and 25 (said release controlling materials present in said extended release layer are biodegradable and selected from the group consisting of...) of the claims that were most recently

examined by the Examiner. The claims of this application state clearly that the release controlling materials are present in the extended release layer of the composition and are biodegradable. The release controlling materials as included in the claims are not the nonbiodegradable, inert, polymeric matrix as described in and required by Saslawski et al.

The Examiner states on page 6 of the Official Action of December 18, 2009 that HPMC (hydroxypropylmethyl cellulose) used in Saslawski et al as well as in the instant invention is in overlapping concentration ranges, therefore irrespective of what HPMC may be called it should render the same effect or benefit. The Examiner further argues that Saslawski et al teach 0.5 to 25% wt binder such as HPMC (page 11, lines 25-28, page12, lines 3-7) therefore HPMC in Saslawski et al., and the instant invention would be expected to yield the same effect or benefit since the invention teach overlapping concentration ranges for HPMC.

In the Response to the Official Action of **January 22, 2009**, it was explained and evidence was filed to support that in spite of using overlapping concentration of HPMC at the lower of the range, the subject matter of invention as claimed herein is clearly distinct from Saslawski et al. A copy of Muhammad Khan Sarfraz et al. paper, "Naproxen Release from Sustained Release Matrix System and Effect of Cellulose Derivatives" Pak. J. Pharm. Sci., 2006, Vol 19 (3), 244-251, which describes that low viscosity grades of HPMC are inappropriate for sustaining the release profiles of naproxen was filed as well as pages 346-349 of the "Handbook of Excipients"; Raymond C Rowe; 5th Edition, Published by Pharmaceutical Press, 2006, Page no. 346-349"

According to Sarfraz, hydrophilic polymer HPMC of low viscosity grades has been used for preparing the sustained release formulation of naproxen. In this study, HPMC has been used either alone or combination with ethyl cellulose (EC) polymer (See table 1). In Formulations F1-F4 HPMC has been used alone (20%-65%) without using another polymer while in formulations

F9-F12 wherein HPMC has been used (1%-3%) in combination with EC (5%). The other formulations F5-F8 no HPMC has been used; only ethyl cellulose polymer has been used for preparing the sustained release formulation of naproxen. The *in-vitro* dissolution studies of all formulations were also performed in this study to predict the achievable plasma drug level. The author of the study discussed that the low viscosity HPMC-based tablets (as used in F1-F4) containing 20%-65% HPMC releases almost 100% of the drug in about 4 hours and rate of drug release could not be sustained for more than 4 hours. Hence, low viscosity grades of HPMC are inappropriate for sustaining the release profiles of naproxen (See fig1). But when HPMC-EC mixture was used wherein the amount of HPMC is 1%, 1.5%, 2%, 3% and the amount of EC is 5%, showed a decreased release rate of naproxen. The release rate of naproxen in eight hours was 38%, 86%, 98 100% from the formulation containing 1%, 1.5%, 2%, 3% HPMC respectively.

By submitting the evidence of comparison of two dissolution profile of two kinds of formulations- (i) Percentage release rate of F1-F4 wherein HPMC has been used alone (20%-65%) without using another polymer (ii) Percentage release rate of F9-F12 wherein HPMC has been used (1%-3%) in combination with EC (5%); it can be inferred that alone low viscosity grade HPMC is not appropriate for sustaining the release of drug. As described in the Handbook of Excipients HPMC is available in different grades and viscosities which can be used as a tablet binder, film-coating and as a matrix for use in extended-release tablet formulation depending upon viscosity, concentration and molecular weight grades. Concentration between 2% and 5% w/w may be used as a binder in wet- and dry-granulation. High viscosity grades may be used to retard the release of drugs from a matrix at level of 10-80% w/w in tablet or capsules while low-viscosity grades are used for film forming and binder.

Saslawski et al., has not disclosed different grades or viscosity of HPMC and its use other than as a binder or disintegrator which are different functions from that claimed in the claims at

issue in this appeal. Saslawski et al., describe release of 9 hours (Once-daily dosing) due to the presence of **nonbiodegradable polymer**, not by the presence of binder e.g. HPMC. In all examples of Saslawski et al., HPMC has been used in an amount which acts as a binder, not for sustaining the release of drug for 9 hours to provide once-daily dosing. One skilled in the art would never use HPMC taught by Saslawski et al., for sustaining the release of drug. An ordinary person skilled in the art would never confuse between HPMC as a binder and HPMC as a release controlling material which is well understood to be used based upon its viscosity and molecular weight grades. As known by a person skilled in the art, when HPMC is used as a binder it is used in a particular grade and viscosity which will only function as a binder and not function as a release controlling agent even used in any amount. This is shown in Sarfraz et al. HPMC as a release controlling material has not been used by Saslawski et al. Saslawski's invention describes a composition of a NSAID by utilizing nonbiodegradable polymer as rate controlling material while the claims in this application require a nonbiodegradable polymer.

Evidence is already of record in the prosecution history of this application that describe that these release controlling materials are biodegradable and/or gel or swell and erode in the presence of water. As described above, these release controlling materials differ from those disclosed in Saslawski et al.

Therefore, an HPMC-based formulation prepared according to Saslawski et al., (even used up to 25%) will not provide the same benefit or effect and requires that the formulation contains **nonbiodegradable polymer**. Saslawski et al clearly and specifically teaches away from using hydrophilic/biodegradable polymer for sustaining the release of drug and doing what is claimed in this application. . "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant"

In re Gurley 27 F.3d 551, 553 (Fed. Cir. 1994); *see KSR*, 127 S. Ct. at 1739-40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious).

The composition prepared according to the present invention does not contain any nonbiodegradable polymer but it contains hydrophilic polymers which are biodegradable in nature and/or swellable in water thus, provides once-daily administration of nimesulide.

One of ordinary skill in the art following the teachings of Saslawski et al. would be taught to formulate a composition having first outer layer allowing immediate release of a first active substance (page 2, line 3-26) and a second layer containing a **nonbiodegradable, inert porous polymeric matrix** (page 2, lines 27-30) and that these polymers or copolymers [are] insoluble in water (but not forming a gel either upon immersion in an aqueous medium) (page 22, lines 8-15). One of ordinary skill in the art would find no motivation to provide a formulation as defined in independent Claims 1 and 25 and the process of Claim 11 of nimesulide with single unit fast release layer comprising micronized nimesulide having average particle size below 5 microns and single unit extended release layer comprising micronized nimesulide having average particle size below 5 microns and **biodegradable release controlling materials** selected from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums in an amount effective to control the release of nimesulide from the extended release layer.

Saslawski et al neither teach nor suggest the use of biodegradable material in second layer

(extended release layer) for prolonging the action of NSAIDs, more preferably nimesulide.

The Examiner admits that "Saslawski et al. do not teach nimesulide" (page 8, line 8 of the Official Action of December 18, 2009) and the Examiner again attempts to equate the drug nimesulide with the drug naproxen. There is no basis for the Examiner's statement that according to Skinhoj et al. ('529) naproxen and nimesulide are equivalent. In column 16, line 58-column 17, line 27 of Skinhoj ('529) while there is a list of different types of NSAIDs, naproxen is listed as an arylpropionic acid derivative and nimesulide is included in the category of others (column 17, line 23), not as an arylpropionic derivative as the Examiner states on page 5, lines 18-21 of the Official Action of December 18, 2009. As explained to the Examiner previously, nimesulide and naproxen are two different compounds and have different properties. (See pages 7 to 9 in the Response to Official Action of August 13, 2008)

The Examiner also attempts to rely on the disclosure of nimesulide from the list of NSAID's in Skinhoj et al. ('529) for stating that it would be obvious to substitute nimesulide for naproxen. One skilled in the art has no reasonable expectation of success that all compounds that are classified under a broad category such as "NSAIDs" can all be formulated in the same way. While the applicants' have provided evidence explaining the differences between nimesulide and naproxen, the Examiner has not provided any references or basis to support his statement. One of ordinary skill in the art would not consider that all of the NSAIDs listed in column 16, line 58-column 17, line 27 are equivalent or that anyone could be substituted for another in a formulation. For example one of ordinary skill in the art knows that acetylsalicylic acid is not equivalent to ibuprofen or acematicin so there is no basis for stating that just because two compounds are grouped together under a broad heading of NSAIDs that naproxen and nimesulide are equivalent, that one could be substituted for the other or that they can both be formulated in the same way.

It is emphasized that neither nimesulide nor any other sulfonanilide derivative has been disclosed by Saslawski et al. Skinhoj is cited by the Examiner but as the Examiner admits in the sentence bridging pages 2 and 3 of the Official Action of December 18, 2009, "Skinhoj et al., do not exemplify invention comprising nimesulide in both the immediate release layer and extended release layer plus the claimed release controlling material(s) in the extended release layer." There is no way to combine these references to teach a composition comprising nimesulide in the fast release layer and in the extended release layer wherein said release controlling materials present in said extended release layer are biodegradable. Neither reference teaches biodegradable release controlling materials in an extended release layer and as discussed above neither reference teaches that nimesulide can be substituted for naproxen.

Although Skinhoj et al., describes certain types of NSAIDs, that include nimesulide and naproxen but it does not teach or suggest micronized nimesulide having average particle size below 5 microns. Applicant herein argues that no prior art (either Skinhoj et al. or Saslawski et al.) mention the use of micronized nimesulide having average particle size below 5 microns. (*See Merck & Co., Inc.*, v. *Biocraft Laboratories*, 874 F.2d 804) (CAFC). The claims include (i) 200 mg micronized nimesulide having average particle size below 5 microns and; (ii) release controlling materials of the extended release layer which are biodegradable. The release controlling materials are NOT nonbiodegradable, inert porous polymeric matrix like the copolymers of (meth)acrylic acid derivatives as required by Saslawski et al.

There is no way for one skill in the art to invent the claimed invention given the disclosures of Saslawski and Skinhoj. Saslawski teaches a second layer consisting of **nonbiodegradable, inert porous polymeric matrix** and does not disclose the use of nimesulide. Saslawski et al. does not teach or suggest biodegradable release controlling materials present in said extended release layer.

"All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). When evaluating claims for obviousness under **35 U.S.C. 103**, all the limitations of the claims must be considered and given weight, including limitations which do not find support in the specification as originally filed (i.e., new matter). *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983) *aff'd mem.* 738 F.2d 453 (Fed. Cir. 1984) (Claim to a catalyst expressly excluded the presence of sulfur, halogen, uranium, and a combination of vanadium and phosphorous. Although the negative limitations excluding these elements did not appear in the specification as filed, it was error to disregard these limitations when determining whether the claimed invention would have been obvious in view of the prior art.) (See MPEP 2143.03)

The independent Claims 1, 11 and 25 define a once-a-day controlled release pharmaceutical tablet composition for peroral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises 200 mg micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more release controlling materials in an amount from 8% to 20 % w/w to control the release of said micronized nimesulide from said composition and pharmaceutical excipients from 30% to 60% w/w of the tablet composition, wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable and based on this it is clear that the claims are patentable and not obvious over the cited references.

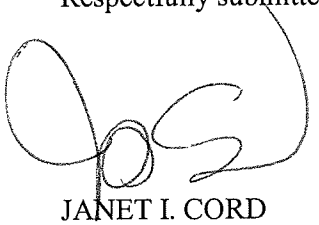
The claims are clearly patentable over Skinhoj et al ., and Saslawski et al., and as such are clearly patentable over these references in combination with Gibson et al. which teaches the use of silicon dioxide.

Neither Skinhoj nor Saslawski et al., nor Gibson et al., singly or in combination, teach or suggest a once-a-day controlled release composition of nimesulide consisting of single unit fast release layer comprising micronized nimesulide having average particle below 5 microns and single unit extended release layer comprising micronized nimesulide having average particle below 5 microns and one or more biodegradable release controlling materials, wherein the release controlling materials present in the extended release layer are specified from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.

Claims 1, 5, 8-11, 19 and 25 are patentable and not obvious over the combined teachings of Skinhoj et al., Saslawski et al., and Gibson et al.

For the above reasons, appellants respectfully request that all rejections of record should be reversed.

Respectfully submitted,



JANET I. CORD
LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO.33778 (212)708-1935

(vii) Claims Appendix

1. A once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises 200mg micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more release controlling materials in an amount from 8% to 20% w/w to control the release of said micronized nimesulide from said composition and pharmaceutical excipients from 30% to 60% w/w of the tablet composition, wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable and are selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.

2. (Cancelled)

3. (Cancelled)

4. (Cancelled)

5. The composition as claimed in claim 1, further comprising release modifiers selected from the group consisting of wetting agents, solubilizers, surfactants, plasticizers, pore formers, pH modifiers and tonicity adjusting agents.

6. (Cancelled)

7. (Cancelled)

8. The tablet composition as claimed in claim 1, wherein the extended release layer further comprises polymers, selected from the group consisting of polycarbophils, carbomers, alginates, cellulose and cellulose derivatives, chitosan gums and lecithins.

9. The tablet composition as claimed in claim 5, wherein the release modifier is a pH modifier and is selected from the group consisting of sodium bicarbonate, hydrochloric acid, citric acid, malic acid, and tartaric acid.

10. The tablet composition as claimed in claim 5, wherein the release modifier is selected from the group consisting of fats, fatty acids and transesterification products of fats and fatty acids with polyols.

11. A process for the manufacture of a once- a-day controlled release tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer, which comprises mixing together micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more release controlling materials in an amount from 8% to 20% w/w to control the release of said micronized nimesulide from said composition and pharmaceutical excipients from 30% to 60% w/w of the tablet composition, wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable and are selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.

Claims 12-18 (cancelled)

19. The composition according to claim 1 wherein the single unit fast release layer comprises micronized nimesulide having average particle size below 5 microns and one or more pharmaceutical excipients selected from diluents, binders, wetting agents, disintegrants and lubricants; and the single unit extended release layer comprises micronized nimesulide having average particle size below 5 microns and biodegradable release controlling material selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose

phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.

Claims 20-24 (cancelled)

25. A once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a coating, a single unit fast release layer and single unit extended release layer, which comprises 200 mg micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more release controlling materials in an amount from 8% to 20% w/w to control the release of said micronized nimesulide from said composition and pharmaceutical excipients from 30% to 60% w/w of the tablet composition, wherein said micronized nimesulide being present in the fast release layer and in the extended release layer and wherein said release controlling materials present in said extended release layer are biodegradable and are selected from the group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.

26. A once-a-day controlled release pharmaceutical tablet composition for per oral administration consisting of a single unit fast release layer and a single unit extended release layer which comprises 200 mg micronized nimesulide having average particle size below 5 microns as an active drug from 20% to 70% w/w of the tablet composition, one or more biodegradable release controlling materials from in an amount from 8% to 20% to control the release of said micronized nimesulide from said composition and pharmaceutical excipients from 30% to 60% w/w of the tablet composition, wherein the fast release layer comprises micronized nimesulide having average particle size below 5 microns, lactose, starch, colloidal silicon dioxide, polyvinylpyrrolidone, polyoxyethylene sorbitan monostearate, docusate sodium, magnesium stearate and croscarmellose sodium; and the extended release layer comprises micronized nimesulide having average particle size below 5 microns, lactose, polyvinylpyrrolidone, magnesium stearate, docusate sodium, hydroxypropyl methylcellulose, colloidal silicon dioxide and sodium lauryl sulphate wherein the hydroxypropyl methylcellulose present in said extended release layer is a biodegradable release controlling material.

(ix) Evidence Appendix

None

(x) Related Proceedings Appendix

None

(xi) Prosecution History Appendix

SUMMARY OF PROSECUTION HISTORY OF
US PATENT APPLICATION 10/089020

This application was filed with the US Patent and Trademark Office on March 25, 2002. **There have been multiple official actions and interviews with the Examiner in order to explain to the Examiner that the claims define a patentable invention that is not anticipated or obvious over any of the references that were cited by the Examiner during prosecution of this application. Furthermore, applicants have submitted multiple declarations and references as evidence of patentability of the claimed invention.**

In the initial Official Action of June 27, 2003, Claims 1-8 and 11-17 were rejected under 35 U.S.C. 102(b) as being anticipated by Singh et al. (US 5,876,751). According to the Examiner Singh teaches a controlled release bilayer tablet comprising 100 mg nimesulide (23%), 203 mg of microcrystalline cellulose (46 %) as cellulose derivative, and 100 mg starch (22%) as excipient. The Examiner referred to column 4, lines 9-14, column 5-6, and Example 3 of Singh. The Examiner also stated that Singh teaches that the control release tablet comprises sodium lauryl sulfate (surfactant), a tablet that is administered orally and a process of manufacturing the control release composition comprising mixing together nimesulide,

In the same action, Claims 1 and 10 were rejected under 35 U.S.C. 102(b) as being anticipated by Sheth et al (US 4,424,235). According to the Examiner Sheth teaches a control release pharmaceutical composition comprising 4 mg hydroxypropylcellulose (1.2%) as the cellulose derivative and hydrogenated cottonseed oil as the fatty acid and reference was made to column 5 Formulation A.

Claims 1 and 9 were rejected under 35 U.S.C. 102(e) as being anticipated by Merrill et al (US 6,077,538). According to the Examiner, Merrill teaches a controlled release

pharmaceutical tablet comprising 10 mg hydroxypropylcellulose (5.3%) as the cellulose derivative and sodium bicarbonate.

In the response to the Official Action, claims 1, 4, 5, 7-11, 15 and 16 were amended and claim 12 was cancelled. It was pointed out that the Singh, Sheth and Merrill did not anticipate the claims because each element of the claims was not disclosed in each of these references.

> *The Examiner has rejected claims 1-8 and 11-17 as being anticipated Singh et al. (US 5,876,751). Applicants respectfully traverse this rejection. Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. In re Paulsen, 30 F.3d 1475, 31 USPQ 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. Scripps Clinic & Res. Found. v.Genentech, Inc., 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991).*
>
> *Singh et al. does not disclose a controlled release pharmaceutical composition of nimesulide. This is clear from the disclosure in col. 8, lines 6-7 of the '751 patent where it is disclosed that the dose administered to the patients was three times daily. One skilled in the art knows that a drug which I administered three times daily is not in a controlled release form. Therefore, since each and every element of the claimed invention is not disclosed in Singh et al. claims 1-8 and 11-17 cannot be anticipated.*
>
> *Therefore, it is respectfully requested that this rejection be withdrawn. The Examiner rejected claims 1 and 10 as being anticipated by Sheth et al. (US Patent 4,424,235). Applicants respectfully traverse this rejection. Sheth et al. cannot anticipate claims 1 and 10 because each and every*

element of the invention claimed in claims 1 and 10 is not disclosed. Claims 1 and 10 of this application define a controlled release pharmaceutical composition of nimesulide. There is no disclosure of nimesulide or controlled release pharmaceutical compositions of nimesulide in Sheth. Although, the disclosure at col. 1, lines 61-64 of Sheth refers to conventional controlled release capsules or tablets containing either L-Dopa alone or a combination of L-Dopa and a decarboxylase inhibitor, there is no disclosure of such compositions. In addition, Sheth does not disclose nor suggests that the properties of nimesulide are similar to those of L-dopa such that any excipient that can be used to prepare a controlled release formulation of LDopa can be used to prepare a controlled release form of nimesulide. Therefore, since each and every element of the claimed invention is not disclosed in Sheth, Sheth cannot and does not anticipate claims 1 and 10.

Therefore, it is respectfully requested that the rejection be withdrawn. The Examiner has rejected claims 1 and 9 under 35 USC 102(e) as being anticipated by Merrill et al. (US Patent 6,077,538). Applicants respectfully traverse this rejection.

As stated above in order for a reference to anticipate each element of the claim must be found in the reference. Merrill does not disclose a composition comprising nimesulide and therefore, Merrill cannot anticipate claims 1 and 9.

In the Official Action of April 21, 2004 which was a final rejection, the Examiner withdrew the rejections over Sheth and Merrill but maintained that claims 1-8, 11, 14-17 were anticipated under 35 U.S.C. 102(b) by Singh et al (US 5,876,751). According to the action, Applicant argues that Singh does not disclose a control release pharmaceutical composition of nimesulide. Applicant argues that the dose was

administered 3 times daily which clearly demonstrates that the dosage was not time released. The Examiner argued that prior art is not required to show in Examples all of the possible compositions and their time-release patterns. The Examiner reiterated that Singh does teach control release (sustained release) of non-steroidal anti-inflammatory drugs including nimesulide. See column 4 lines 9-14.

The Examiner stated that Claims 9 and 10 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art does not teach or suggest the instant invention comprising the instant basic and acidic substances of claims 9 and 10.

In the Response to Office Action, claims 1, 2, 4, 10, 11, 15 and 17 were amended. Claims 13, 14 and 16 were cancelled. It was explained that

> *[t]he basis for the amendments for a controlled release composition for oral administration having a fast release fraction and an extended release fraction with nimesulide being present in the fast release and in the extended release fraction is found at, inter alia, page 8, lines 3-4, 11-13 and examples 10 and 11 of the specification.*
> *Support for the term release controlling materials is based on the fact that the materials are used to control release of the active ingredient.*

It was explained that claims 1-8, 11, and 14-17 were not anticipated Singh et al. (US 5,876,751).

> *Singh et al. discloses specifically a pharmaceutical composition of Diclofenac free acid, Fenpiverinium Bromide and Pitofenone hydrochloride. It does not teach a controlled release formulation of nimesulide as a single active drug in a unit dose. Singh does not disclose that a composition can comprise both a fast*

release fraction and extended release fraction. Singh teaches modified, sustained controlled and timed release formulations. In addition, Singh does not disclose a controlled release pharmaceutical composition of nimesulide which has a fast release fraction and an extended release fraction wherein nimesulide is present in the fast release fraction and in the extended release fraction.

Therefore, since each and every element of the claimed invention is not disclosed in Singh et al. claims 1-8, 11 and 14-17 cannot be anticipated.

An Advisory Action was mailed on November 23, 2004 stating that the amendments to the claims raised new issues that required further consideration and/or a new search. A request for continued examination was filed.

In the Official Action mailed March 28, 2005—the rejections of the claims were all based on 35 USC 112, first paragraph. **No art was cited against the claims**. In the response to this action, claims 1, 2, 4, 6, 7, 8, 9, 10, 11 and 15 were amended and arguments were submitted to overcome these rejections under USC 112, first paragraph.

In the Official Action of March 20, 2006—the rejections under 35 USC 112, first paragraph were withdrawn.

Claims 1, 2, 4-11, and 15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Skinhoj (WO 99/12524). According to the Examiner

Skinhoj teaches a composition of an NSAID for peroral use comprising a fast release layer and an extended release layer, wherein said NSAID is present in both layers and in an amount ranging from 1 to 1600 mg. Skinhoj teaches that such a composition reduces the dose amount of active required on a daily bases [sic] as compared to a plain tablet. Skinhoj teaches that the composition can comprise a control release material such as cellulose derivatives, and excipients,

plasticizers, calcium carbonate and fatty acids. Skinhoj teaches that the composition can exist in tablet form. Skinhoj teaches a number of NSAIDs including nimesulide. See abstract, page 19 line 22 - page 20 line 27, page 21 lines 19-21, page 26 lines 28-29, page 35 lines 15-24, page 36 line 25 - page 38 line 32, claims 1, 11.

The Examiner admitted that Skinhoj does not disclose an example where nimesulide is employed in the composition / tablet. According to the Examiner "[i]t would have been obvious to one having ordinary skill in the art to have employed nimesulide in the tablet / composition. One would have been motivated to do this in order to decrease the dosage amount of nimesulide given to a patient." However, the Examiner did not provide any basis for statement.

In the Response to the Official Action of March 20, 2006, applicants argued

It is not obvious from the disclosure of W099/12524 to one having ordinary skill in art to formulate single unit tablet compositions comprising nimesulide as simple particles in admixture with other excipients; wherein nimesulide is present in both the fast as well as extended release layer. Nowhere in the citation is there disclosure, teaching or suggestions describing compressing the multiple units to a tablet dosage form. The multiple units cannot be formulated into a tablet dosage form since the application of compression force in a tablet compression machine will lead to rupturing of the coated multiple units resulting in loss of uniformity of the coating layer over the entire unit (pellet or granule) thus producing variable and unpredictable release of the active agent from such compressed forms, if at all it is made into such form. The invention claimed in this application involves the simple treatment of nimesulide with the excipients and then compressing them into tablets.

The claimed product is easy to formulate and does not involve the cumbersome step of producing pellets and further coating them to obtain units for producing sustained release of the drug. The claimed invention is specifically a layered tablet composition wherein one layer i.e. the extended release layer comprises a release controlling polymer and the other layer is a fast release layer wherein nimesulide is present in both the fast as well as extended release layer.

Moreover, the compositions disclosed in the above cited reference relate specifically to lornoxicam (Refer to page 27, lines 4-7, page 53, lines 11-12 and examples 1-18, pages 53-83 of the cited reference). It is not taught in the citation to select from a large class of NSAIDs, a specific drug i.e. nimesulide which can be made into a ready-to-use single unit tablet dosage form that can be administered to the patient directly. The citation discloses only multiple units, which need to be first formulated into a suitable dosage form prior to administration to a patient. Nowhere, in the citation is provided a composition or particularly a method to formulate the multiple units into a specific ready-to-use dosage form such as tablet, capsule etc

.

It is known to a person skilled in art that multiple units such as pellets stated in the citation are essentially formulated as capsules, not compressed into tablets, primarily due to associated problems during compression of such multiple units such as rupture of units or the coating leading to a batch-to-batch variation in drug release. It is not obvious from the citation to one having ordinary skill in art to formulate controlled release layered tablet compositions of Nimesulide by seeing just the mere disclosure in the citation from such a large class of NSAIDs which have widely varying physicochemical properties such as solubility, flowability, particle size, pKa, permeability, therapeutic dose requirements, pharmacokinetics, etc. PCT publication WO 99/12524

relates specifically to preparation of pellets (Refer particularly page 17, lines 33-34 of the cited reference and refer page 31, lines 31-35 of the cited reference). PCT publication WO 99/12524 further discloses that when appropriate, the first fraction is coated into homogeneous pellets (Refer page 17, lines 33-34 of the cited reference) and the second fraction comprises multiple units which are coated with a sustained release coating designed to release the drug substance in such a manner that the maintenance of a therapeutically active plasma concentration for a relatively long period of time are obtained (Refer page 1, lines 14-17 of the cited reference).

Furthermore, compositions and processes disclosed in the cited reference relate specifically to preparation of pellets as well as coating on pellets (Refer page 53, lines 11-12 of the cited reference) and preparation of granulates (Refer page 31, lines 2-4 of the cited reference and refer page 53, lines 10-11 of the cited reference). It is important to note that preparation and coating of pellets or granulates is a very cumbersome and cost intensive process. Further, a person skilled in art is neither taught nor motivated to form tablets from multiple units since it is disadvantageous to compress different fractions of multiple units, as the compression of such coated multiple units into tablets causes fracturing of particularly the coating layer, thereby causing loss of reproducibility. Instead, the claimed invention specifically relates to tablet compositions comprising Nimesulide along with sustained release polymers, wherein the said polymers are used for coating the tablets which is the final dosage form thus preventing any fracture of coating or the dosage form, which in turn enhances batch-to-batch reproducibility and provides uniform drug release from the matrix tablet.

With regards to examiner's comments that it would have been

obvious to one having ordinary skill in the art to have employed Nimesulidein the tablet/composition and one would have been motivated to do this in order to decrease the dosage amount of Nimesulide given to the patient, we beg to differ with the examiner's comments as the formulation of a tablet dosage form instead of multiple units does not lead to any change in the dosage amount of Nimesulide; instead the former being a single unit dosage form is easy to administer to a patient. Furthermore, PBI's invention has additional benefit with regards to patient compliance as the single unit tablet dosage form is a ready-to-use dosage form as compared to the multiple units disclosed in the cited reference since the multiple units such as pellets essentially have to be formulated into a single unit dosage form before administration.

In the Official Action of October 23, 2006, the Examiner stated that although he had considered the arguments filed July 25, 2006, he did not consider them to be persuasive.

The rejection of claims 1,2,4-11, and 15 under 35 USC 103(a) as being obvious over WO 99/12524 was maintained.

The Examiner stated that "WO ' 524 teaches numerous NSAID's including nimesulide that can be present in both the fast and extended release portions of the multi-unit composition."

The Examiner stated that "the general teaching of WO' 524 suggests that all NSAID's disclosed therein can be formulated into a multi-unit composition wherein the same NSAID can be present in both the fast and extended release layers; thus, a reading of the examples to lornoxicam does not limit the invention to multi-unit compositions comprising only lornoxicam."

Prior to filing a response to the Official Action of October 23, 2006, a telephone interview was held with the Examiner in order to discuss the claims and the cited reference WO 99112524. Claims 1 and 11 along with proposed amendments to these claims were discussed. Following this a request for continued examination was filed and claims 1 and 11 were amended and claims 18-25 were added.

In the response to the Official Action it was argued that WO 99/12524 does not set forth a *prima facie* case of obviousness for the invention.

> *Claims 1 and 11 have been amended to define the fast release layer and the extended release layer as single unit layers. In WO 99/12524 it is disclosed that the first and second fractions comprise multiple units (see the abstract, line 4; page 1, line 10-15; page 6, lines 10-12; and page 6, line 25-page 10.) A tablet of single unit layers is not obvious from a reference that discloses fractions that comprise multiple units such as pellets.*
>
> *The formulation of multiple units into a single unit tablet, for example, a tablet of a fast release layer and an extended release layer, is not possible technically because the application of the force required to compress a tablet in a tablet compressing machine will lead to rupturing of the multiple units resulting in loss of uniformity thus producing variable and unpredictable release of the active ingredient, e.g. nimesulide. A natural consequence of this, is batch-to-batch variation. Therefore, it is clear that one skilled in the art considering this reference would not have a reasonable expectation that a controlled release pharmaceutical tablet composition of nimesulide made of single unit layers can be prepared.*

In the Official Action of July 27, 2007, the Examiner stated that "Claims 1, 2, 4-11, 15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Skinhoj (WO 99/12524; 3/18/99). New claims 18,19 and 25 are added to this rejection."

According to the Examiner Skinhoj:

> *teaches a composition of an NSAID for peroral use comprising a fast release layer and an extended release layer, wherein said NSAID is present in both layers and in an amount ranging from 1 to 1600 mg. Skinhoj teaches that such a composition reduces the dose amount of active required on a daily bases as compared to a plain tablet. Skinhoj teaches that the composition can comprise a control release material such as cellulose derivatives, and excipients, plasticizers, calcium carbonate and fatty acids. Skinhoj teaches that the composition can exist in tablet form. Skinhoj teaches a number of NSAIDs including nimesulide. Skinhoj teaches that the fractions (fast release layer and extended release layer) can be coated.*

According to the Examiner Skinhoj did not disclose "an example where nimesulide is employed in the composition." Without providing any legitimate basis for his statement, the Examiner stated that it would have been obvious to one having ordinary skill in the art to have employed nimesulide in the tablet / composition.

The Examiner noted the applicants' claim amendments of claims 1 and 11 to define the immediate release layer and controlled release layer as single unit layers to distinguish from Skinhoj. The Examiner argued " that multiple units are not excluded from the instant invention since the instant invention employs 'comprising' language."

The Examiner also included that "Claims 20-24 were objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art

does not teach or suggest the instant invention comprising the fast release and slow release layers as defined in the claims."

Telephone interviews were held with the Examiner on October 10 and 22, 2007. During the interviews, a number of claims were discussed, including claims 1, 11, 18 and 20-24.

In the response to the Official Action, claims 1, 2, 4, 5, 8, 9, 10, 11, 15, 19, and 25 were amended and claims 26-30 were added.

Applicants explained that "Claims 1 and 11 have been amended to define that composition consists of a single unit fast release layer and a single unit extended release layers. Based on the Examiner's comments on page 3 of the action and the discussions held with applicants' representative that claims 1 and 11 as amended herein and the claims dependent thereof are distinguished from W099/12524".

Although the Examiner had indicated during the interview held prior to filing the response that the claims were allowable, **another Official Action was mailed on February 7, 2008**.

The Examiner's statements concerning the withdrawn rejections under 35 USC 103(a) were inconsistent. The Examiner found that the applicant's arguments were persuasive and withdraw the rejection over Skinhoj (WO 99/12524) because Claims 1 and 11 were amended to define the immediate release layer and controlled release layer as single unit layers and a tablet of single units layers is not obvious from WO '524 that discloses fractions that comprise multiple units such as pellets. The Examiner argues that multiple units are excluded from the instant invention since the instant invention employs "consisting of" language.

On April 16, 2008, another telephone interview was held with the Examiner to discuss the claims and Skinhoj (WO99/12524) . Proposed claim amendments were discussed. It was discussed that the rejection over Skinhoj (WO 99/12524) was withdrawn.

In the response to the Official Action of February 7, 2008, claims 2, 4, 5, 8, 9, 10, 15, 19 and 25 were amended. Arguments were also presented to overcome the rejections under 35 USC 112, first and second paragraphs, that were made in the Official Action of February 7, 2008.

Again, this response was not followed by a Notice of Allowance but by another Official Action (mailed August 13, 2008).

The Examiner stated that "Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection."

In this action, Claims 4, 5, 7-10, 15, and 19 were rejected under 35 U.S.C. 112, first paragraph.

The Examiner rejected Claims 1, 2, 4, 5, 8-11, 15, 19, and 25-30 under 35 U.S.C. 103(a) as being unpatentable over Saslawski et al. (WO 99/33448) in view of Gibson et al. (US 6426340) based on US Provisional 60/018202; 5/23/96).

According to the Examiner:

> *Saslawski et al. teach a multilayer tablet that can be made up of only two layers, i.e. a first layer (immediate or fast release layer) and second layer (prolonged release layer containing a nonbiodegradable, inert porous polymeric matrix [emphasis added]). See page 2 lines 19-30. Saslawski et al. teach that both layers can contain the same active ingredient (page 4*

lines 14-16). Saslawski et al. teach a wide selection of actives for the tablet including the instant nimesulide (naproxen). See page 4 line 14 - page 5 line 10. Saslawski et al. teach that fast and prolonged release layers can comprise wetting agents, pH regulators, lactose, starch, polyvinylidone, polyoxyethylene sorbitan monostearate, docusate sodium, magnesium stearate and croscarmellose. In addition to the above specified ingredients the prolonged release layer can comprise hydroxypropyl methylcellulose and sodium lauryl sulfate. See page 9 line 10- page 12. Saslawski et al teach that the tablet can be polymer film coated (page 15 lines 3-6, page 19 lines 12-15). Saslawski et al. do not exemplify a tablet comprising specifically nimesulide as the active along with all of the ingredients listed above. However, Saslawski et al. do suggest such a combination of ingredients. Saslawski et al. also do not teach the tablet comprising colloidal silicone dioxide. However, Gibson et al. teach that colloidal silicone dioxide is a common excipient used in immediate and controlled released tablet formulations (USPN '340 column 4 lines 47-60). Therefore, it would have been obvious to one having ordinary skill in the art to modify the invention of Saslawski et al. to include the silicone dioxide. One would have been motivated to do this since the silicone dioxide is a common excipient employed in immediate and control release formulations.

A personal interview was held with the Examiner on October 7, 2008 and as shown by the attached summary it was stated that "Agreement with respect to the claims was reached" because WO99/33448 does not disclose nimesulide. During the interview the structural formulas of nimesulide and naproxen were given to the Examiner for the purpose of showing that these are two different compounds.

In the Response to the Official Action, claims 1, 2, 4, 5, 8-11, and 25-30 were amended.

It was explained why the rejections under 35 USC 112 should be withdrawn.

The response included the structures of naproxen and nimesulide to show that the compounds are chemically distinct. References were also submitted to support the arguments concerning the difference between naproxen and nimesulide and the differences that result in the need to prepare different formulations.

It was explained that:

> *Naproxen is a member of the 2-arylpropionic acid (profen) family of NSAIDs. It is an odorless, white to off-white crystalline substance. It is lipid-soluble and practically insoluble in water. While nimesulide, chemically 4'-nitro-2'-phenoxy methane sulfonanilide, is a weakly acidic non-steroidal anti-inflammatory drug which is sparingly soluble in water. It differs from other non-steroidal anti-inflammatory drugs (NSAIDs) in that its chemical structure contains a sulfonanilide moiety as the acidic group rather than a carboxylic group. It exhibits a significant selectivity toward cyclooxygenase-2 (COX-2) versus COX-1 inhibition, which may explain the lower incidence of gastric side effects. It was also explained that the active substances disclosed in WO 99/33448 have different physicochemical properties; some are soluble, some insoluble, some show pH-dependent solubility and some do not (See page no. 4, line nos. 17-38 to page 8, line 29 of the cited publication). The substances have different physico-chemical properties such as solubility, effective dose, pKa, permeability, etc. and hence require specific formulation strategies in terms of natureand quantity of excipients used and/or process parameters. For example among NSAIDs, diclofenac sodium as disclosed in W099/33448 has high aqueous solubility and is easy to formulate. In addition, the NSAIDs on page 5, lines 6-21 are described as arylpropionic derivatives, arylacetic derivatives, anthranilic derivatives, indole derivatives, oxicams, pyrazole containing derivatives and indene derivatives. Sulfonanilides as a class are not included in this list. Hence,*

different active substances with different properties cannot have the same generalized formulation as disclosed in the cited publication. Nimesulide is practically insoluble in water and difficult to formulate. (See WO 91117774 -Page no. 1, Second Paragraph lines 6-20, especially line No. 15-20 of the same paragraph); WO 99/41233 (Page no.l, second paragraph lines 6-12, especially line no. 9-12 of the same paragraph.); Nalluri, B.N. et al., AAPS PharmSciTech 2003; 4(1) Articles 2 (Page no. 1 second column under heading "INTRODUCTION" line 12-25); and Piel, G., Pirotte, B., Delneuville, 1. et al "Study of the influence of both cyclodextrins and L-lysine on the aqueous solubility of nimesulide; Isolation and characterization of nimesulide-L- lysine-cyclodextrin complexes"; Journal of Pharmaceutical Sciences Volume 86, Issue 4, April 1997, Pages 475-480.)

It was explained that the invention "provides a formulation specifically for nimesulide which is a poorly water soluble active substance along with release controlling materials" ***[emphasis added].***

The claimed composition is a once-a-day controlled release pharmaceutical tablet composition. The claimed composition comprises a single unit fast release layer and a single unit extended release layer wherein nimesulide, from the fast release layer, provides immediate benefit to the patient and from the extended release layer, provides benefit to the patient for a longer duration.

W099/33448 was discussed and it was explained that it does not disclose nor suggest a once-a-day controlled release composition.

For example, Example 1 of W09933448 discloses that Eudragit® is used in concentration of 8.80% and Example 3 of the cited reference discloses that Eudragit® is used in concentration of 10, 8.8 and 8.8% (page no. 20, line nos. 22 to 27; page no. 23, line nos. 26 to 31; page no. 24, line nos. 1

to 14 of the cited publication)]. Figures 1-6 all show dissolution in 9 hours or less.

The material used in W099/33448 is not sufficient to prolong the release of active substance for a considerably longer duration of time; thus it does not provide any teaching about once-a- day composition of nimesulide. Therefore the formulation disclosed in the PCT publication cannot be considered as prolonged release formulation in the true sense.

It was also argued that WO '448 does not provide any suggestion or motivation for one skilled in the art to replace an active drug described in the reference with nimesulide to prepare a controlled release pharmaceutical tablet composition of nimesulide consisting of a single unit fast release layer and a single unit extended release layer to provide once-daily dosing of nimesulide; especially given the problems associated with preparing a formulation of nimesulide.

It was also argued that US Patent 6,426,340 discloses silicon dioxide as a common excipient used in immediate and controlled release tablet formulation and the combination of WO '448 and US '340 does not teach multilayered or bilayered tablet of nimesulide as claimed in this invention.

In the present case, there is no suggestion of a once-a-day formulation of nimesulide; no reasonable expectation of success in formulating a once-a-day tablet composition of nimesulide and all of the claim limitations (e.g. once-a-day tablet composition) are not disclosed in the reference. A once-a-day formulation solves a long-felt need for a once-a-day tablet composition of nimesulide. The difficulties in developing a once-a-day tablet composition of nimesulfide were discussed above.

The Examiner issued another Official Action dated January 22, 2009.

The Examiner stated that the applicant's arguments were not persuasive and repeated the rejection from the previous action (Claims 1, 2, 4, 5, 8-11, 15, 19, and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saslawski et al. (WO 99/33448; 7/8/99) in view of Gibson et al. (US 6426340; 7/30/02) based on US Provisional 60/018202; 5/23/96.

The Examiner agreed that Nimesulide is not disclosed in WO '448, that it is distinct from Naproxen recited in the office action and Naproxen is not a NSAID compound like Nimesulide. The Examiner agreed with the Applicants' statement.

However, The Examiner stated that

> *WO '448 allows for the inclusion of NSAID compounds which would suggest the inclusion of Nimesulide (or the Sulfonanilide compound class). Although WO '448 does not specifically disclose Nimesulide or other sulfonanilides, WO '448 provides examples of NSAID compounds. Specifically note, WO '448 provides examples of NSAIDs such as or for example arylpropionic derivatives (page 5 lines 6-21). The use of the language such as/for example allows for the inclusion of NSAID compounds like Nimesulide which are not specifically recited in WO '448.*

The Examiner again noted that WO' 448 does not disclose Nimesulide specifically or as a class.

> *Applicants also argue that Nimesulide is a NSAID compound falling within the Sulfonanilide class. Although WO '448 discloses NSAID compounds, the reference does not recite the use of the sulfonanilide class of compounds like Nimesulide. WO '448 does not suggest the use of Nimesulide. The Examiner argues that WO '448 allows for the inclusion of NSAID compounds which would suggest the inclusion of Nimesulide (or*

the Sulfonanilide compound class). Although WO '448 does not specifically disclose Nimesulide or other sulfonanilides , WO '448 provides examples of NSAID compounds.

Applicants use WO 91/17774, WO 99/41233, Nalluri et al and Piel et al to point out that Nimesulide is practically insoluble in water and difficult to formulate. On the other hand, instant invention provides a formulation for poorly water soluble nimesulide with release controlling materials. The Examiner argues that WO '448 at page 4 lines 17-38 to page 8 line 29 employ a wide range of active substances having a wide range of solubility properties - some soluble some insoluble, some showing pH-dependent solubility and some not showing pH-dependent solubility. The references referred to by the Applicants disclose that Nimesulide is practically insoluble in water. WO '448 teaching that a wide range of actives in terms of solubility properties can be employed makes it obvious to include the poorly water soluble nimesulide.

WO '448 does not disclose or suggest a once-a-day controlled release composition as recited in the amended claims. WO '448 shows composition dissolution in a max of 9 hours in the Figures. WO '448 does not disclose the materials that would prolong the release of the active substance for a longer period of time. The Examiner argues that WO '448 suggests the same combination of ingredients with NSAID compounds as recited in instant claims (see 103(a) rejection above). Therefore, it obvious that WO '448 yields a formulation that has prolonged release of the active. WO '448 does not have to exemplify all scenarios of the disclosed formulation in order to render instant once a day/prolonged formulation obvious.

Applicants' representative held a Personal Interview with the Examiner on April 1, 2009 and representatives of applicants participated from India by telephone. During

the interview the claims, proposed claim amendments, WO 99/33448 and the advantages of the invention were discussed.

Following the interview, a response was filed.

Claim 1 was amended to include release controlling materials that were included in claim 4 and the phrase cellulose and cellulose derivatives was replaced by the cellulose derivatives included in the paragraph bridging pages 9 and 10 of the specification.

It was explained that the release sustaining materials as referred to on page 6 of the specification are release controlling materials and support for the said release sustaining materials as release controlling materials is provided in pages 8 and 9 of the specification. A release sustaining material is a material that will control the release of a compound. This is also supported by original claims 1 and 11.

The Examiner's continued rejection of claims 1, 2, 4, 5, 8-11, 15, 19 and 25-30 under 35 U.S.C. 103(a) as being unpatentable over Saslawski et al (W099/33448) in view of Gibson et al (US6426340) based on US Provisional Application 60/018202 was noted and it was again argued that the rejection was improper and should be withdrawn. It was also noted that the application had been pending since 2003.

It was explained:

> *As amended, claim 1 now defines a once-a-day controlled release tablet composition consisting of single unit fast release layer comprising nimesulide and single unit extended release layer comprising nimesulide and one or more release controlling materials in an effective amount to control the release of nimesulide from said composition and wherein the release controlling materials are selected from a group consisting of*

methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate. cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides.

It was also explained that:

The amount of the release controlling material(s) present in the extended release layer is effective to control the release of nimesulide from said layer.

The release controlling materials of the composition do not act as binders or disintegrants. It was also explained that the release controlling materials included in the claims do not include non-biodegradable, inert, polymeric matrix as described in Saslawski et al.

Claim 26 was amended to include hydroxy propyl methylcellulose as the release controlling material which distinguishes this from the hydroxypropyl methylcellulose or other cellulose derivatives used in Saslawski et al which are used as either disintegrants. Reference was made to Saslawski et al. page 9, lines 21-24 (disintegrant) or as binder (See page 12, lines 3-7) and not as release rate controlling material. It was explained that support for the amendment to claim 26 is based on the disclosure in the last paragraph on page 9 and Example 10.

It was also argued that:

The claimed composition that includes these rate controlling materials is not obvious in view of the disclosure of Saslawski et al.

Saslawski et al. teach a multilayer tablet that can be made up of only two layers i.e. a first layer (immediate or fast release layer) and second layer (prolonged release layer containing a nonbiodegradable, inert porous polymeric matrix). See page 2, lines 19-30. Saslawski et al teach that the second layer constitutes an inert matrix that does not become eroded and does not swell in an aqueous medium (See page 3, line 33-35) and that the essential constituents of the second prolonged-release layer are polymeric materials which confer on it its inert and nonbiodegradable character. The polymers or copolymers are insoluble in water, not forming a gel and are discharged intact by the body (See page 12, lines 10-15).

The polymeric matrix of the second layer in Saslawski et al. are in particular polyvinyl chlorides, vinyl acetate copolymers and copolymers of (meth) acrylic acids, which are further specifically described and are commercially available as Eudragit® polymers (See page 12 and 13).

Saslawski et al. specifically teaches use of such a nonbiodegradable inert polymeric matrix in the second layer, which are conferred by polymers of methacrylic acid derivatives or copolymers of (meth)acrylic acids (Eudragit® series), to ensure release of the active ingredient independently of the influence of the body (and in particular pH variations) (See page 19, lines 1-25). All examples illustrated in Saslawski et al. utilize Eudragit series of polymers (methacrylic acid derivatives) to achieve prolonged release of active ingredient. It is noted that Saslawski et al neither teach nor suggest the use of biodegradable material in second layer (extended release layer) for prolonging the action of NSAIDs, more preferably nimesulide.

It was argued that:

Saslawski et al. teach away from Claim 1, as amended herein. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant" In re Gurley 27 F.3d 551, 553 (Fed. Cir. 1994); see KSR, 127 S. Ct. at 1739-40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious).

One of ordinary skill in the art following the teachings of Saslawski et al. would be taught first outer layer allowing immediate release of a first active substance (page 2, line 3-26) and a second layer containing a non biodegradable, inert porous polymeric matrix (page 2, lines 27-30) and that these polymers or copolymers [are] insoluble in water (but not forming a gel either upon immersion in an aqueous medium) (page 22, lines 8-15). One of ordinary skill in the art would find no motivation to provide a formulation as defined in independent claims 1, 11 and 25 and dependent claim 19 of nimesulide with single unit fast release layer comprising nimesulide and single unit extended release layer containing release controlling materials selected from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides in an amount effective to control the release of nimesulide from the extended release layer.

References were submitted with the response that describe that these release controlling materials are biodegradable and/or gel or swell and erode in the presence of

water. It was explained that these release controlling materials differ from those disclosed in Saslawski et al.

The following information was provided that supports that the release controlling materials used in the claimed invention are biodegradable unlike those used in Saslawski that are not biodegradable.

1) Cellulose and cellulose derivatives: R. Chandra, Renu Rustgi, Biodegradable Polymers, Prog. Poly. Sci. Vol. 23, 1273-1335, 1998, Section 2.1 -Second paragraph and Section 2.1.2

2) Gelatin: R. Chandra, Renu Rustgi, Biodegradable Polymers, Prog. Poly. Sci. Vol. 23,
1273-1335, 1998, Section 2.2.1

3) Polyalkylene polyols (polyethylene glycols): Bernhard et al. Water Research 42 (2008), 4791-4801, whole article and conclusion. A printout from Wikipedia was also submitted that describes that polyethylene glycol and polyethylene oxide are the same.

4) Gum Arabic: Ramakrishnan et al., Biosource Technology 98 (2007):368-372. See abstract.

5) Xanthan gum: S. Rosalam et al., Enzyme and Microbial Technology 39 (2006) 197-207.

It was once again explained to the Examiner that disclosure of NSAIDs in Saslawski et al. does not suggest nimesulide or any other sulfonanilide derivative.

While Saslawski et al. on page 5, lines 6-20, describes certain types of NSAIDs, those that include aryl propionic acid derivatives, aryl acetic acid derivatives, aryl carboxylic acid derivatives, anthranilic derivatives, and indole derivatives it does not "teach" NSAIDs that are sulfonanilide derivatives and does not teach or suggest nimesulide.

It was explained that Claim 1:

> *specifically recites the release controlling materials of the extended release layer to be selected from a group consisting of methyl cellulose, ethylcellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides most of which are hydrophilic in nature and which hydrate and swell in presence of water or body fluids, thus the release controlling materials are NOT nonbiodegradable, inert porous polymeric matrix like the copolymers of (meth)acrylic acid derivatives as required by Saslawski et al.*
>
> *This clearly distinguishes the present invention from the teachings of Saslawski et al. which neither teaches nor suggests a once-a-day controlled release tablet composition of a single unit fast release layer comprising nimesulide and a single unit extended release layer comprising nimesulide and one or more release controlling materials selected from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose ,hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate, hydroxypropyl*

methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides.

Although it is disclosed on page 9, line 10 and page 12 that the prolonged release layer of Saslawski et al. can comprise hydroxypropyl methylcellulose and sodium lauryl sulfate, the hydroxypropyl methylcellulose or other cellulose derivatives (like carboxymethyl cellulose) and carbomers used in Saslawski et at, are being used as either disintegrating agent (See page 9; lines 21-24) or as binder (See page 12; lines 3-7) but not as a release controlling material, which is how it is being used in the compositions of nimesulide of this invention.

During the interview held on April 1, 2009; Examiner indicated that the amount of release controlling material in the range 5% to 65% w/w on page 5 of the specification and claim 2 of present invention overlaps with the range of 0 to 15% by weight of disintegrating agent disclosed on page 9, lines 19-20 of the Saslawski, et al. and considered that the release controlling material may act as a disintegrating agent in the said range. Applicant again explained by including the definitions of binder and disintegrant that these terms differ in meaning from the term release controlling material as used by applicant in amended claims 1, 11,15, 19, 25 and 26.

Reference was made to Rudnic et al. Chapter 92 Oral Solid Dosage Forms, Remington: The Science and Practice of Pharmacy; Vol 11, 19th Edition, Mack Publishing Company, Pennsylvania 1995. Pages No. 1615-1620, which defines the terms binder and disintegrants.

According to Rudnic (Page no 1617; first paragraph under binder); binders are the agents which impart cohesive quality to the powdered materials. They generally impart cohesiveness to the tablet formulation

which insures the tablet remaining intact after compression as well as improving the free-flowing property by the formulation of granules of desired hardness and size. Material commonly used as binder includes starch, gelatin, and sugars as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums which have been used include acacia, sodium alginate, and extract of Irish Moss, Panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Vegum and arabogalactan. Other agents that can be used as binders are polyethylene glycol, ethylcellulose, waxes, water and alcohol.

One of ordinary skill in the art very well understands the role and functions of binders. Binders are generally used in an amount only to provide sufficient binding to the matrix material and are used as additives in the formulation (these do not contribute as release controlling materials).

Rudnic further provides the definition of disintegrator at page no 1619; according to Rudnic; disintegrator is a substance, or a mixture of substances added to a tablet to facilitate its breakup or disintegration after administration. The active ingredient must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution. Materials serving as disintegrants have been classified chemically as starches, clays, cellulose, alginates, gums and cross-linked polymer.

However, while present composition of nimesulide comprises gums (either synthetic or natural), gelatin, alginates, carbomers, polyalkylene polyols, polycarbophils, polyethylene oxides and cellulose derivative, these are used as a rate controlling material not as binders and disintegrants.

The present composition of nimesulide comprises an effective amount of release controlling material which controls the release of drug over a period of time. The effective amount of said release controlling material as claimed in claim 1 can be in the range between 0.1 % w/w to 99% w/w, (or 5% w/w to 65% w/w as in claim 2) of the total composition provided that the said release controlling materials significantly contribute to control the release of drug over a period of time. With respect to Saslawski et al; the amount of disintegrating agent is in the range between 0 to 15% and acts as a disintegrating agent regardless of the amount of said disintegrating agent. Saslawski et al do not disclose that the use of 'such disintegrating agents in a particular amount or ratio may act as a release controlling material. While in present invention applicant uses release controlling material in an effective amount to control the release of nimesulide from said composition.

It was again explained that Saslawski et al does not teach use of cellulose and cellulose derivatives, and carbomers as release controlling materials as has been described in the claims 1, 11, 19, 25 and 26. It was argued that the "mere disclosure of hydroxypropyl methylcellulose and sodium lauryl sulphate in Saslawski et al does not teach or suggest their use as release controlling materials".

It was clearly explained why the claimed invention is not obvious Saslawski et al, and that no *prima facie* showing of obviousness has been made.

As further evidence to support that the claimed invention is not obvious over Saslawski et al.. The declaration of Dr. Rajesh Jain, one of the inventors of the claimed subject matter was filed with the response. Dr. Jain describes experiments that were conducted that establish the advantages of the claimed invention compared to an immediate release composition of nimesulide and a composition comprising Diclofenac. Dr. Jain also describes the commercial success of the claimed invention.

The osteoarthritis treatment paradigm was described.

First-line treatment options for OA (acetaminophen and lifestyle recommendations) are successful to a limited extent. Patients typically shift to either traditional NSAIDs or selective COX-2 inhibitors as second-line therapy. Some patients may progress further and require treatment for flare-ups (corticosteroids, hyaluronic acid) or invasive surgery. Non-steroidal anti-inflammatory drugs (NSAIDs) have been widely available for decades. Due to their well-established efficacy and dosing profile, they remain commonly used agents for mild-to-moderate OA. However, they may cause serious GI side effects with long-term use. Long-term use of any of the traditional NSAIDs, may damage the mucous layer of the stomach, resulting in general stomach discomfort or, more seriously bleeding and ulcer formation.

Selective COX-2 inhibitors are a subset of NSAIDs that specifically inhibit the COX-2 enzyme. The intent of this specificity is to reduce GI side effects commonly associated with the traditional NSAIDs. However, the COX-2 class has been associated with a higher incidence of cardiovascular side effects.

Physicians make their treatment choice based on four primary factors since comparative studies have found no clear efficacy differences:

-
-

Dosing and Frequency
Gastrointestinal Risks
Cardiovascular Risks
Renal Risks

Physicians must balance the different risks based on individual patient circumstances – but none of the current therapies provide the combination of simplified dosing with minimal GI, cardiovascular and renal risks.

Dr. Jain explained why nimesulide extended release tablet is positioned to meet the identified unmet needs with current therapeutics for the treatment of osteoarthritis (OA) and explained the commercial success of the product. Panacea Biotec's brand Willgo®, based on the present invention (bilayered, controlled release Nimesulide tablets), sold in India, has been proven to be a highly effective product for the management of chronic OA pain and inflammation. The tablet offers the advantage of once a day dosing with favorable GI tolerability and good safety in cardio vascular and renal parameters. Panacea's product was introduced in India as a new drug delivery product supported by promising clinical trial results. The product was able to address a significant unmet medical need which resulted in consistently growing sales. The IMS-ORG audited data for the December 2006-December 2008 was submitted.

From this data, it can be concluded that the sales growth of Willgo® (Extended Release Nimesulide) is increasing year by year. The percentage growth of sales of Willgo® increased by 80.8% in the two years from December 2006 to December 2008. While percentage sales growth of Nimulid® Tablet (Immediate Release Nimesulide) has increased only by 8.25% in the two years from December 2006 to December 2008 and decreased by 3.4% in last one year from December 2007 to December 2008.

It was stated in the response that:

The decision on patentability must be made based upon consideration of all the evidence including the evidence submitted by the examiner and the evidence submitted by the applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence. Facts established by rebuttal evidence must be

evaluated along with the facts on which the conclusion of obviousness was reached, not against the conclusion itself. In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990). Therefore, the Examiner must consider the evidence in Dr. Jain's declaration and the evidence of commercial success.

There is no suggestion or motivation in the combination of the cited references to combine the references to develop a once-a-day controlled release composition of nimesulide as claimed in this application and no reasonable expectation of success to achieve its success in the market place.

Neither Saslawski et al nor Gibson et al., singly or in combination, teach or suggest a once-a-day controlled release composition of nimesulide consisting of single unit fast release layer comprising nimesulide and single unit extended release layer comprising nimesulide and one or more release controlling materials and wherein the release controlling materials are specified from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate. cellulose acetate propionate. cellulose acetate trimellitate. Cellulose carboxymethyl ethers and their salts. hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, gums and polyethylene oxides.

In yet another Office Action (mailed July 20, 2009), the Examiner found that Applicant's arguments with respect to claims have been considered but are moot in view of the new ground(s) of rejection.

The Examiner rejected Claims 1, 2, 5, 8-11, 15, 19, 25, 26 and 31 are rejected under 35 U.S.C. 1 03(a) as being unpatentable over Skinhoj et al (US 6599529; 7/29/03), Saslawski et al. (WO 99/33448; 7/8/99) in view of Gibson et al. (US 6426340; 7/30/02) based on US Provisional 60/018202; 5/23/96). According to the Examiner:

> *Skinhoj et al teach a once a day oral pharmaceutical modified release multiple-units formulation (column 21 lines 34-53) comprising NSAID compounds including nimesulide and naproxen (claim 9). Skinhoj et al teach two fractions of multiple units wherein both fractions contain the about 5% to about 50% NSAID (column 11 lines 1-10). Skinhoj et al teach that the first fraction can contain sodium carbonate (column 20 lines 10-31). Skinhoj et al teach that individual units containing the NSAID are coated with 1-20% coating (column 22 lines 32-53). The film forming agents include ethylcellulose and colloidal silica (column 22 line 66 - column 23, line 12). The coating is an admixture of excipients and colloidal silicium dioxide (column 23 lines 57-60). The coating for the outer second layer may comprise substances such as ethylcellulose, and hydroxypropyl metthylcellulose (column 24 lines 15-44).*
>
> *Skinhoj et al. do not exemplify invention comprising nimesulide in both the immediate release layer and extended release layer plus the claimed release controlling material(s) in the extended release layer. Saslawski et al. teach a multilayer tablet that can be made up of only two layers, i.e. a first layer (immediate or fast release layer)and second layer (prolonged release layer containing a nonbiodegradable, inert porous polymeric matrix). See page 2 lines 19-30. Saslawski et al. teach that both layers can contain the same active ingredient (page 4 lines 14-16). Saslawski et al. teach a wide selection of actives for the tablet including the instant nimesulide (naproxen). See page 4 line 14 - page 5 line 10. Saslawski et al. teach that fast and prolonged release layers can comprise wetting*

agents, pH regulators, lactose, starch polyvinylidone, polyoxyethylene sorbitan monostearate, docusate sodium, magnesium stearate and croscarmellose. In addition to the above specified ingredients the prolonged release layer can comprise hydroxypropyl methylcellulose and sodium lauryl sulfate. See page 9 line 10- page 12. Saslawski et al teach that the tablet can be polymer film coated (page 15 lines 3-6, page 19 lines 12-15). Saslawski et al. do not exemplify a tablet comprising specifically nimesulide as the active along with all of the ingredients listed above. However, Saslawski et al. do suggest such a combination of ingredient.

The Examiner responded to Applicants' Argument

Applicants argue that Nimesulide is not disclosed in WO '448. Nimesulide is distinct from Naproxen recited in the office action. Naproxen is not a NSAID compound like Nimesulide. The Examiner agrees with the Applicants' statement [emphasis added]. However, it is important to note that WO '448 allows for the inclusion of NSAID compounds which would suggest the inclusion of Nimesulide (or the Sulfonanilide compound class). Although WO '448 does not specifically disclose Nimesulide or other sulfonanilides, WO '448 provides examples of NSAID compounds. Specifically note, WO '448 provides examples of NSAIDs such as or for example arylpropionic derivatives (page 5 lines 6-21). The use of the language such as/for example allows for the inclusion of NSAID compounds like Nimesulide which are not specifically recited in WO '448.

Applicants also argue that Nimesulide is a NSAID compound falling within the Sulfonanilide class. Although WO '448 discloses NSAID compounds, the reference does not recite the use of the sulfonanilide class of compounds like Nimesulide. WO '448 does not suggest the use of Nimesulide. The Examiner argues that WO '448 allows for

the inclusion of NSAID compounds which would suggest the inclusion of Nimesulide (or the Sulfonanilide compound class). Although WO '448 does not specifically disclose Nimesulide or other sulfonanilides , WO '448 provides examples of NSAID compounds.

Specifically note, WO '448 provides examples of NSAIDs such as or for example arylpropionic derivatives (page 5 lines 6-21). The use of the language such as/for example allows for the inclusion of NSAID compounds like Nimesulide which are not specifically recited in WO '448.

Applicants use WO 91/17774, WO 99/41233, Nalluri et al and Piel et al to point out that Nimesulide is practically insoluble in water and difficult to formulate. On the other hand, instant invention provides a formulation for poorly water soluble nimesulide with release controlling materials. The Examiner argues that WO '448 at page 4 lines 17-38 to page 8 line 29 employ a wide range of active substances having a wide range of solubility properties - some soluble some insoluble, some showing pH-dependent solubility and some not showing pH-dependent solubility. The references referred to by the Applicants disclose that Nimesulide is practically insoluble in water. WO '448 teaching that a wide range of actives in terms of solubility properties can be employed makes it obvious to include the poorly water soluble nimesulide. WO '448 does not disclose or suggest a once-a-day controlled release composition as recited in the amended claims. WO '448 shows composition dissolution in a max of 9 hours in the Figures. WO '448 does not disclose the materials that would prolong the release of the active substance for a longer period of time. The Examiner argues that WO '448 suggests the same combination of ingredients with NSAID compounds as recited in instant claims (see 103(a) rejection above). Therefore, it obvious that WO '448 yields a formulation that has prolonged release of the active. WO '448 does not have to exemplify all scenarios of the disclosed formulation in order to

render instant once a day/prolonged formulation obvious.

The Examiner argued that USPN '340 is used for the sole purpose of showing that silicon dioxide is a common excipient used in
immediate and controlled release tablet formulations.

The Examiner noted that the Applicants argued that "the hydroxypropyl methylcellulose is used in the instant invention as a release controlling material, which is distinguished from the HPMC used in Saslawski et al as a disintegrant or as a binder rather than as a release rate controlling material as disclosed in the instant invention, and that the Applicants argued that Saslawski et al. uses specifically nonbiodegradable
inert material in the second layer. Saslawski et al. do not teach or suggest the use biodegradable material in the second layer for the purpose of prolonging active NSAID (nimesulide). The terms nonbiodegradable and biodegradable adds no patentable weight to the instant claims since there is no recitation of either term in the claims. The instant claims do not make claim to non biodegradable material or biodegradable material. **The Examiner acknowledges the references provided by the Applicants to support that instant release controlling materials are biodegradable. The Examiner reiterates that there is no recitation in the instant claims that the release controlling material is biodegradable.**

The Examiner noted that Saslawski et al. do not teach nimesulide and that Skinhoj et al. teach use of both naproxen and nimesulide and suggest that both naproxen and nimesulide are equivalent. The Examiner provided no support for this.

The Examiner referred to the declaration showing results for the nimesulide 200 mg tablet in Example 10 with respect to efficacy, safety, osteoarthritis and sales. The Examiner would like to point out that although the results may be true for the nimesulide 200 mg tablet in Example 10, the claims are not commensurate in scope with Example 10. In fact, Applicants do not provide any results for the tablet of claim 1 wherein nimesulide is present in both an immediate release layer and extended release layer. The

extended release layer comprises one or more release controlling agent/material. For this reason the results provided by way of the declaration are not applicable for overcoming the rejection cited above. The Examiner reiterates that the claims are not commensurate in scope with tablet of Example 10.

Another interview was held with the Examiner on 21 July 2009.

In the response to this action, claims 1, 11, 19, 25 and 26 were amended.

Claims 1, 5, 8-11, 19, 25 and 26 are pending in this application and claims 1, 5, 8-11, 19, and 25 are the claims on appeal.

It was explained that none of the prior art of Skinhoj et al (US6599529), Saslawski et al (W099/33448) in view of Gibson et al (US6426340) based on US Provisional Application 60/018202 do not mention the use of 200mg micronized nimesulide having average particle size below 5 microns in fast release layer and extended release layer of the claimed composition and that the claims have been restricted to the dose of micronized nimesulide i.e. percentage amount of micronized nimesulide, release controlling materials and pharmaceutical acceptable excipients which is in the range from 20 to 70% w/w, 8% to 20% w/w and 30% to 60% w/w respectively of the total composition.

It was explained that the release controlling materials are now clearly mentioned as being present in the extended release layer of the claimed composition and are biodegradable in nature, and the release controlling materials as included in the claims do not include non-biodegradable, inert, polymeric matrix as described in Saslawski et al.

It was also explained that polymers such as cellulose carboxymethyl ether and their salts and polyethylene oxide were deleted from claim 1 as rate controlling polymers to address the Examiner's concern that that the claim to a tablet comprising nimesulide in the

extended release and the immediate release layer wherein polymer (control release material) is in the extended release layer, is not commensurate in scope with the results provided for 200 mg nimesulide tablet in Example 10.

It was again explained that the release controlling materials of the claimed composition do not act as binders or disintegrants and these rate controlling materials are not obvious in view of the disclosure of Saslawski et al.

> *Saslawski et al. teach a multilayer tablet that can be made up of two layers i.e. a first layer (immediate or fast release layer) and second layer (prolonged release layer containing a non biodegradable, inert porous polymeric matrix). See page 2, lines 19-30. Saslawski et al teach that the second layer constitutes an inert matrix that does not become eroded and does not swell in an aqueous medium (See page 3, line 33-35) and that the essential constituents of the second prolonged-release layer are polymeric materials which confer on it its inert and nonbiodegradable character. The polymers or copolymers are insoluble in water, not forming a gel and are discharged intact by the body (See page 12, lines 10-15).*

The applicants expressed their views along with supportive evidence for the purpose of showing that HPMC used by Saslawski would not result in the same benefit or effect as obtained by present invention.

The following references were brought to the Examiner's attention:

> 1) Muhammad Khan Sarfraz et al, "Naproxen Release from Sustained Release Matrix System and Effect of Cellulose Derivatives" Pak. J. Pharm. Sci.,2006, Vol 19 (3), 244-251, which provides the teaching that low viscosity grades of HPMC are inappropriate for sustaining the release profiles of naproxen and

2) "Handbook of Excipients"; Raymond C Rowe; 5th Edition, Published by Pharmaceutical Press, 2006, Page no. 346-349".

It was explained that according to Sarfraz, et al.:

hydrophilic polymer HPMC of low viscosity grades has been used for preparing the sustained release formulation of naproxen. In this study, HPMC has been used either alone or combination with ethyl cellulose (EC) polymer (See table 1). In Formulations FI-F4 wherein HPMC has been used alone (20%-65%) without using another polymer while in formulations F9-F12 wherein HPMC has been used (1 %-3%) in combination with EC (5%). The other formulations F5-F8 wherein no HPMC has been used; only ethyl cellulose polymer has been used for preparing the sustained release formulation of naproxen. The in-vitro dissolution studies of all formulations were also performed in this study to predict the achievable plasma drug level. The author of the study discussed that the low viscosity HPMC-based tablets (as used in F I-F4) containing 20%-65% HPMC releases almost 100% of the drug in about 4 hours and rate of drug release could not be sustained for more than 4 hours. Hence, low viscosity grades of HPMC are inappropriate for sustaining the release profiles of naproxen (See Figure 1). But when HPMC-EC mixture was used wherein the amount of HPMC is 1 %, 1.5%, 2%, 3% and amount of EC is 5%, showed a decreased release rate of naproxen. The release rate of naproxen in eight hours was 38%, 86%, 98 100% from the formulation containing 1 %, 1.5%, 2%, 3% HPMC respectively. By submitting the evidence of comparison of two dissolution profile of two kinds of formulations- Percentage release rate of F I-F4 wherein HPMC has been used alone (20%-65%) without using another polymer (ii) Percentage release rate of F9-F12 wherein HPMC has been used (l %-3%) in combination with EC (5%); we infer that alone low viscosity grade HPMC is not appropriate for sustaining the release of

drug. As evidently known by Handbook of Excipients that HPMC is available in different grades and viscosities which can be used as a tablet binder, film-coating and as a matrix for use in extended-release tablet formulation depending upon viscosity, concentration and molecular weight grades. Concentration between 2% and 5% w/w may be used as a binder in wet- and dry-granulation. High viscosity grades may be used to retard the release of drugs from a matrix at level of 10-80% w/w in tablet or capsules while low-viscosity grades are used for film forming and binder.

Moreover, Saslawski et al has not disclosed different grades or viscosity of HPMC and its use other than binder or disintegrator. Saslawski et al provide release of 9 hours (Once-daily dosing) due to the presence of non-biodegradable polymer, not by the presence of binder e.g. HPMC. In all examples of Saslawski, HPMC has been used in an amount which acts as a binder, not for sustaining the release of drug for 9 hours to provide once-daily dosing.

It was explained that a person skilled in the art:

would never use HPMC taught by Saslawski for sustaining the release of drug. Therefore, HPMC-based formulation prepared according to Saslawski (even used up to 25%) will not provide the same benefit or effect until formulation contains additional non-biodegradable polymer. Saslawski et al teaches away from using hydrophilic/biodegradable polymer for sustaining the release of drug.

The composition prepared according to the present invention does not contain any non-biodegradable polymer but also it contains hydrophilic polymers which are biodegradable in nature and/or swellable in water thus, provides once-daily administration of nimesulide.

The inventors insist that person skilled in the art would never confuse between HPMC as a binder and HPMC as a release controlling material which is well understood to be used based upon its viscosity and molecular weight grades. As known by a skilled person, when HPMC is referred to be used as a binder it is used in the particular grade and viscosity which will only function as a binder and not function as a release controlling agent even used in any amount as shown in Sarfraz.

Applicants argued that the Examiner was speculating "*his own understanding over the prior art teaching which is not intended and mentioned in the prior arts. In doing this, the Examiner is engaging in impermissible hindsight*".

In all examples of Saslawski, HPMC has been used in an amount which acts as a binder, not for sustaining the release of drug for 9 hours to provide once-daily dosing. Hence person skilled in the art would never use HPMC taught by Saslawski for sustaining the release of drug. Therefore, HPMC-based formulation prepared according to Saslawski (even used up to 25%) will not provide the same benefit or effect until formulation contains additional nonbiodegradable polymer. Saslawski et al teaches away from using hydrophilic/biodegradable polymer for sustaining the release of drug.

The Examiner states on page 4 of the Office Action that Saslawski et al. allows for the inclusion of NSAID compounds which would suggest the inclusion of Nimesulide (or the sulfonanilide compound class). The Examiner argues on page 5 of the Office Action *"Skinhoj el al. teach use of naproxen and nimesulide and suggest that both naproxen and nimesulide are equivalent. For this reason, it would have been obvious to artisan in the field to modify the invention of Saslawski et al. by substituting the naproxen taught therein with the nimesulide taught by Skinhoj et al."*

It is emphasized that neither nimesulide nor any other sulfonanilide derivative has been disclosed by Saslawski et al. Although Skinhoj et at. describes certain types of NSAIDs, that include nimesulide and naproxen but it does not teach or suggest micronized nimesulide having average particle size below 5 microns.

It was reiterated in the response that the Examiner must consider the evidence in Dr. Jain's declaration and the evidence of commercial success.

It was again explained that there is no suggestion or motivation in the combination of the cited references to combine the references to develop a once-a-day controlled release composition of nimesulide as claimed in this application and no reasonable expectation of success to achieve its success in the market place.

> *Neither Skinhoj nor Saslawski et al nor Gibson et al., singly or in combination, teach or suggest a once-a-day controlled release composition of nimesulide consisting of single unit fast release layer comprising micronized nimesulide having average particle below 5 microns and single unit extended release layer comprising micronized nimesulide having average particle below 5 microns and one or more biodegradable release controlling materials, wherein the release controlling materials present in the extended release layer are specified from a group consisting of methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, carbomers, polyalkylene polyols, polycarbophils, gelatins, and gums.*

The last action is discussed in the Argument section of this Appeal Brief.